WE CLAIM:

1. A host cell that comprises:

a) a solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene; and

b) a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide;

wherein expression of the target polypeptide in an insoluble form causes a change in expression of the reporter gene.

2. The host cell of claim 1, wherein the solubility responsive promoter comprises a polynucleotide sequence that is at least 75% identical to a polynucleotide selected from the group consisting of SEQ ID NOS:1-22.

3. The host cell of claim 2, wherein the solubility responsive promoter comprises a polynucleotide selected from the group consisting of SEQ ID NOS:1-22.

4. The host cell of claim 1, wherein the solubility responsive promoter comprises a polynucleotide that comprises a regulatory region of a gene listed in Table 1.

5. The host cell of claim 1, wherein the solubility responsive promoter comprises a polynucleotide that comprises an RpoH recognition site.

6. The host cell of claim 5, wherein the solubility responsive promoter comprises a polynucleotide that is at least 75% identical to a polynucleotide selected from the group consisting of SEQ ID NOS:23-43.

7. The host cell of claim 6, wherein the solubility responsive promoter comprises a polynucleotide selected from the group consisting of SEQ ID NOS:23-43.

8. The host cell of claim 1, wherein the solubility responsive promoter is upregulated when the target polypeptide is expressed in insoluble form.

9. The host cell of claim 1, wherein the solubility responsive promoter is downregulated when the target polypeptide is expressed in insoluble form.

10. The host cell of claim 1, wherein the polynucleotide that encodes the target polypeptide is heterologous to the host cell.

11. The host cell of claim 1, wherein the target protein-expressing nucleic acid comprises a promoter operably linked to the polynucleotide that encodes the target polypeptide.

12. The host cell of claim 11, wherein the target protein-expressing nucleic acid comprises a promoter that is heterologous to the host cell.

13. The host cell of claim 11, wherein the target protein-expressing nucleic acid comprises a promoter that is heterologous to the polynucleotide that encodes the target polypeptide.

14. The host cell of claim 1, wherein the protein solubility responsive promoter is a prokaryotic promoter.

15. The host cell of claim 14, wherein the protein solubility responsive promoter is a Gram negative bacterial promoter.

16. The host cell of claim 15, wherein the Gram negative bacterium is a member of the family Enterobacteriaceae.

17. The host cell of claim 16, wherein the member of the family Enterobacteriaceae is selected from the group consisting of the genera *Escherichia, Salmonella, Shigella, Klebsiella* and *Enterobacter*.

18. The host cell of claim 17, wherein the Gram negative bacterium is *E. coli*.

19. The host cell of claim 14, wherein the protein solubility responsive promoter is a Gram positive bacterial promoter.

20. The host cell of claim 1, wherein the protein solubility responsive promoter is a eukaryotic promoter.

21. The host cell of claim 20, wherein the promoter is a mammalian, plant, insect, fungal, or yeast promoter.

22. The host cell of claim 1, wherein the reporter gene comprises a polynucleotide that encodes a selectable or detectable polypeptide.

23. The host cell of claim 22, wherein the selectable or detectable polypeptide is selected from the group consisting: a metabolic enzyme, antibiotic resistance factor, a chemiluminescent protein, and a fluorescent protein.

24. The host cell of claim 23, wherein the detectable polypeptide is β-galactosidase.

25. The host cell of claim 23, wherein the detectable polypeptide is a luminescent or fluorescent protein.

26. The host cell of claim 22, wherein the reporter gene further comprises a polynucleotide that encodes a signal peptide that directs the detectable polypeptide to a surface of the host cell.

27. The host cell of claim 26, wherein the reporter gene further comprises a molecular tag that facilitates separation of a host cell that expresses the reporter gene from a host cell that does not express the reporter gene.

28. The host cell of claim 1, wherein the protein solubility responsive promoter is from the same species as is the host cell.

29. The host cell of claim 1, wherein the target polypeptide comprises a fragment of a larger polypeptide.

30. The host cell of claim 29, wherein the fragment comprises a domain of the larger polypeptide.

31. The host cell of claim 30, wherein the domain is identified by homology to other polypeptides, by hydropathy plot, or both.

32. The host cell of claim 29, wherein the fragment comprises a polypeptide encoded by a random fragment of a polynucleotide that encodes the larger polypeptide.

33. The host cell of claim 1, wherein the target polypeptide comprises a mutated form of a polypeptide.

34. An array of two or more populations of host cells of claim 1, wherein the host cells of each population differ in the target polypeptides expressed by the host cells.

35. The array of claim 34, wherein the polypeptides differ due to amino acid substitutions, deletions, or insertions compared to a reference amino acid sequence.

36. The array of claim 34, wherein the target polypeptides expressed by the populations of host cells comprise different fragments of a larger polypeptide.

37. A method of determining the solubility of a target polypeptide, the method comprising:

a) culturing a host cell of claim 1 under conditions in which the target polypeptide is expressed; and

b) determining whether expression of the reporter gene is increased or decreased, thereby determining the solubility of the expressed target polypeptide.

38. The method of claim 37, wherein the host cell is a prokaryotic cell.

39. The method of claim 38, wherein the host cell is an *E. coli* cell.

40. The method of claim 37, wherein the solubility responsive promoter comprises a polynucleotide sequence that is at least 75% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NOS:1-43.

41. The method of claim 40, wherein the solubility responsive promoter comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOS:1-43.

42. The method of claim 37, wherein the host cell is a eukaryotic cell.

43. The method of claim 37, wherein expression of the reporter gene is determined by performing a quantitative assay to determine the amount of detectable or selectable polypeptide in the cell.

44. The method of claim 37, wherein the host cells are subjected to cell sorting to separate cells having increased or decreased expression of the reporter gene from cells in which expression of the target polypeptide does not change the expression level of the reporter gene.

45. The method of claim 44, wherein the reporter gene encodes a fluorescent protein and the cell sorting comprises fluorescence activated cell sorting.

46. The method of claim 37, wherein:

the solubility reporter nucleic acid further comprises:

a) a polynucleotide that encodes a molecular tag; and

b) a polynucleotide that encodes a signal peptide;

wherein the signal polypeptide, the molecular tag, and a detectable or selectable polypeptide encoded by the reporter gene are expressed as a fusion protein and the signal polypeptide directs the detectable or selectable polypeptide to a surface of the cell;

and the method further comprises contacting host cells with a solid support to which the molecular tag can bind, wherein cells that express the reporter gene are immobilized on the solid support.

47. The method of claim 46, wherein the solubility responsive promoter is downregulated when the target polypeptide is expressed in insoluble form, and host cells that express the target polypeptide in insoluble form do not bind to the solid support.

48. The method of claim 46, wherein the solubility responsive promoter is upregulated when the target polypeptide is expressed in insoluble form, and host cells that express the target polypeptide in insoluble form bind to the solid support.

49. The method of claim 46, wherein the molecular tag comprises an epitope for an antibody, a poly-histidine tag, or a FLAG™ peptide.

50. The method of claim 37, wherein the method further comprises:

lysing the host cells under nondenaturing conditions after expressing the target polypeptide, wherein the target polypeptide is in a liquid phase if expressed in soluble form, and in a solid phase if expressed in insoluble form; and

determining the amount of soluble target polypeptide in the liquid phase.

51. The method of claim 50, wherein the target polypeptide comprises a molecular tag and the method further comprises:

removing an aliquot of the liquid phase after lysing the cells; and

contacting the target polypeptide with a detection reagent that binds to the molecular tag to determine the amount of soluble target polypeptide in the liquid phase.

52. The method of claim 51, wherein the molecular tag comprises an epitope for an antibody, a poly-histidine tag, or a FLAG™ peptide.

53. The method of claim 51, wherein the aliquot is placed on a solid support to which the target polypeptide binds prior to contacting the polypeptide with the detection reagent.

54. The method of claim 53, wherein the solid support is composed of a material selected from the group consisting of glasses, plastics, polymers, metals, metalloids, ceramics, and organics.

55. The method of claim 54, wherein the solid support comprises a microtiter plate, a nitrocellulose membrane, a nylon membrane, a derivatized nylon membrane, or an agarose particle.

56. A method of identifying mutations in a cell that alter the solubility of a target polypeptide comprising:

a) treating a cell with a mutagen;

b) introducing into the cell:

i) a solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene; and

ii) a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide;

c) culturing the cell under conditions favorable for expression of the target polypeptide;

d) measuring expression of the reporter gene; and

e) comparing the level of expression of the reporter gene in the cell with the level observed in an unmutated cell that comprises the solubility reporter nucleic acid and the target polypeptide-expressing nucleic acid to identify a cell that comprises a mutation that alters the solubility of the target polypeptide.

57. The method of claim 56, wherein the cell is treated with the mutagen after introducing either or both of the solubility reporter nucleic acid and the target polypeptide-expressing nucleic acid into the cell.

58. The method of claim 56, wherein the cell is a prokaryotic cell.

59. The method of claim 58, wherein the cell is an *E. coli* cell.

60. The method of claim 56, wherein the cell is a eukaryotic cell.

61. The method of claim 56, wherein the solubility is altered to enhance solubility.

62. The method of claim 56, wherein the solubility is altered to decrease solubility.

63. A method for identifying alterations to a polynucleotide that encodes a target polypeptide that alter the solubility of the target polypeptide, the method comprising:

a) altering a polynucleotide that encodes the target polypeptide to form an altered polynucleotide;

b) introducing into a cell:

i) a solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene; and

ii) a target polypeptide-expressing nucleic acid that comprises the altered polynucleotide;

c) culturing the cell under conditions favorable for expression of the target polypeptide;

d) measuring the expression of the reporter gene; and

e) comparing the level of expression of the reporter gene with the level observed in a cell with an unaltered polynucleotide that encodes the target polypeptide, to identify an alteration to the polynucleotide that changes the solubility of the encoded target polypeptide.

64. A method to identify variations in a process for biosynthesis of a target polypeptide that alter the solubility of the target polypeptide, the method comprising:

culturing a host cell under alternative conditions in which the target polypeptide is expressed, wherein the host cell comprises:

a) a solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene; and

b) a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide;; and

comparing the expression of the reporter gene by host cells grown under each of the alternative conditions.

65. The method of claim 64, wherein at least two cells are cultured and the expression of the reporter gene in each cell is compared, thereby identifying a cell that expresses an altered amount of soluble target polypeptide.

66. The method of claim 64, wherein the protein solubility responsive promoter is upregulated if the target polypeptide is expressed in insoluble form, and expression of the reporter gene at a lower level is indicative of a process condition that results in greater expression of soluble target polypeptide.

67. A method of screening an expression library to identify library members that express soluble target polypeptide, the method comprising:

a) introducing a plurality of expression vectors that each comprise a polynucleotide that encodes a target polypeptide into a plurality of host cells to create an expression library, wherein the host cells comprise a solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene;

b) culturing the host cells under conditions in which the target polypeptides are expressed; and

c) detecting expression of the reporter gene, thereby identifying library members that express soluble target polypeptides.

68. The method of claim 67, wherein the protein solubility responsive promoter is upregulated when the target polypeptide is expressed in insoluble form, and host cells that express soluble target polypeptides express the reporter gene at a decreased level compared to host cells that express insoluble target polypeptides.

69. The method of claim 67, wherein the protein solubility responsive promoter is downregulated when the target polypeptide is expressed in insoluble form, and host cells that express soluble target polypeptides express the reporter gene at an increased level compared to host cells that express insoluble target polypeptides.

70. The method of claim 69, wherein the reporter gene comprises a selectable marker and host cells are grown under selective conditions, thereby selecting for host cells that express soluble target polypeptides.

71. A method of identifying an antibiotic agent, the method comprising:

contacting a cell that comprises a solubility reporter nucleic acid with a candidate antibiotic agent, wherein the solubility reporter nucleic acid comprises a protein solubility responsive promoter operably linked to a reporter gene; and

detecting the level of expression of the reporter gene, wherein a change in the expression level of the reporter gene in a cell contacted with the candidate antibiotic agent, compared to reporter gene expression level in a cell which is not contacted with the candidate antibiotic agent, is indicative of an agent that inhibits protein folding in the cell.

72. The method of claim 71, wherein the protein solubility responsive promoter comprises a polynucleotide that comprises a regulatory region of a gene listed in Table 1.

73. A method of identifying a promoter that is differentially regulated in response to expression of an insoluble polypeptide in a host cell that comprises the promoter, the method comprising:

a) providing a host cell that comprises:

i) a solubility reporter nucleic acid that comprises a putative protein solubility responsive promoter operably linked to a reporter gene; and

ii) a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide;

b) culturing the host cell under conditions in which the target polypeptide is expressed in insoluble form; and

c) determining whether expression of the reporter gene is increased or decreased, thereby determining whether the putative protein solubility responsive promoter is differentially regulated in response to expression of an insoluble polypeptide in the host cell.

74. The method of claim 73, wherein the putative protein solubility responsive promoter is a heat shock promoter.

75. The method of claim 73, wherein the putative protein solubility responsive promoter is a eukaryotic promoter.

76. The method of claim 73, wherein the putative protein solubility responsive promoter is a prokaryotic promoter.